Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis

Paul E Ronksley, doctoral student,1 Susan E Brien, post-doctoral fellow,1 Barbara J Turner, professor of medicine and director,2 Kenneth J Mukamal, associate professor of medicine,3 William A Ghali, scientific director and professor1,4

ABSTRACT
Objective To conduct a comprehensive systematic review and meta-analysis of studies assessing the effect of alcohol consumption on multiple cardiovascular outcomes.

Design Systematic review and meta-analysis.


Inclusion criteria Prospective cohort studies on the association between alcohol consumption and overall mortality from cardiovascular disease, incidence of and mortality from coronary heart disease, and incidence of and mortality from stroke.

Studies reviewed Of 4235 studies reviewed for eligibility, quality, and data extraction, 84 were included in the final analysis.

Results The pooled adjusted relative risks for alcohol drinkers relative to non-drinkers in random effects models for the outcomes of interest were 0.75 (95% confidence interval 0.70 to 0.80) for cardiovascular disease mortality (21 studies), 0.71 (0.66 to 0.77) for incident coronary heart disease (29 studies), 0.75 (0.68 to 0.81) for coronary heart disease mortality (31 studies), 0.98 (0.91 to 1.06) for incident stroke (17 studies), and 1.06 (0.91 to 1.23) for stroke mortality (10 studies). Dose-response analysis revealed that the lowest risk of coronary heart disease mortality occurred with 1–2 drinks a day, but for stroke mortality it occurred with ≥1 drink per day. Secondary analysis of mortality from all causes showed lower risk for drinkers compared with non-drinkers (relative risk 0.87 (0.83 to 0.92)).

Conclusions Light to moderate alcohol consumption is associated with a reduced risk of multiple cardiovascular outcomes.

INTRODUCTION
Possible cardioprotective effects of alcohol consumption seen in observational studies continue to be hotly debated in the medical literature and popular media. In the absence of clinical trials, clinicians must interpret these data when answering patients’ questions about taking alcohol to reduce their risk of cardiovascular disease. Systematic reviews and meta-analyses have addressed the association of alcohol consumption with cardiovascular disease outcomes but have not uniformly addressed associations between alcohol use and mortality from cardiovascular disease, as well as the incidence and mortality from coronary heart disease and stroke. Additionally, further studies have been published since 2006, when the most recent reviews appeared. The continuing debate on this subject warrants an in-depth reassessment of the evidence.

In this paper, we synthesise results from longitudinal cohort studies comparing alcohol drinkers with non-drinkers for the outcomes of overall mortality from cardiovascular disease, incident coronary heart disease, mortality from coronary heart disease, incident stroke, and mortality from stroke. Because of the many biological effects of alcohol consumption, we also examine the association of alcohol with mortality from all causes when this is reported in studies. We conducted meta-analyses for each of these outcomes and a sensitivity analysis with lifetime abstainers as the reference category to account for the heterogeneity within the reference group of non-drinkers. We also examined the effect of confounding on the strength of observed associations. In our companion paper, we link these cardiovascular outcomes with experimental trials of alcohol consumption on candidate causal molecular markers.

METHODS
Data sources and searches
We performed a systematic review and meta-analysis following a predetermined protocol in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines. We identified all potentially relevant articles regardless of language by searching Medline (1950 through September 2009) and Embase (1980 through September 2009) supplemented by manual searches of bibliographies and conference proceedings.
Fig 1  Details of study selection for review

2009). Searches were enhanced by scanning bibliographies of identified articles and review articles, as well as reviewing conference proceedings from three major scientific meetings (American Heart Association, American College of Cardiology, and European Heart Congress) between 2007 and 2009. Experts in the field were contacted regarding missed, ongoing, or unpublished studies.

To search electronic databases, we used the strategy recommended for systematic reviews of observational studies.19 We specified three comprehensive search themes:

- To identify relevant terms related to the exposure of interest (theme 1), the first Boolean search used the term “or” to explode (search by subject heading) and map (search by keyword) the medical subject headings “ethanol” or “alcohol” or “alcoholic beverages” or “drinking behaviour” or “alcohol drinking” or text words “drink$” or “liquor$” or “ethanol intake” or “alcohol$ drink$” or “ethanol drink$”
- To identify relevant outcomes (theme 2), a second Boolean search was performed using the term “or” to explode and map the medical subject headings “stroke” or “cardiovascular diseases” or “myocardial infarction” or “myocardial ischemia” or “coronary artery disease” or “heart infarction” or text words “cv$” or “infarct$” or “isch$” or “cvd$” or “ami” or “ihd” or “cad”
- To identify relevant study designs (theme 3), a final Boolean search using the term “or” to explode and map the medical subject headings “cohort studies” or “follow-up studies” or “incidence” or “prognosis” or “early diagnosis” or “survival analysis” or text words “course” or “predict$” or “prognos$” was performed.

These three comprehensive search themes were then combined using the Boolean operator “and” in varying combinations.

Study selection
Two individuals (SEB and PER) independently reviewed all identified abstracts for eligibility. All abstracts reporting on the association between alcohol intake and cardiovascular disease events were selected for full text review. This stage was intentionally liberal. We discarded only those abstracts that clearly did not meet the aforementioned criteria. The inter-rater agreement for this review was high ($κ =$0.86 [95% confidence interval 0.80 to 0.91]). Disagreements were resolved by consensus.

The same reviewers performed the full text review of articles that met the inclusion criteria and articles with uncertain eligibility. Articles were retained if they met the inclusion criteria for study design (prospective cohort design), study population (adults ≥18 years old without pre-existing cardiovascular disease), exposure (current alcohol use with a comparison group of non-drinkers), and outcome (overall cardiovascular disease mortality or atherothrombotic conditions, specifically incident coronary heart disease, coronary heart disease mortality, incident stroke, or stroke mortality). Both published and unpublished studies were eligible for inclusion. Authors were contacted if the risk profile of the cohort was unclear.

Data extraction and quality assessment
The primary exposure variable was the presence of active alcohol drinking at baseline compared with a reference group of non-drinkers. Because of the heterogeneity of this reference group, we identified the subset of studies using lifetime abstainers as the reference group and studies that distinguished former drinkers from non-drinkers. Whenever available, we extracted information on amount of alcohol consumed, using grams of alcohol per day as the common unit of measure. When a study did not specifically report the grams of alcohol per unit, we used 12.5 g/drink for analysis.11 We standardised portions as a 12 oz (355 ml) bottle or can of beer, a 5 oz (148 ml) glass of wine, and 1.5 oz (44 ml) glass of 80 proof (40% alcohol) distilled spirits. Volume of intake was categorised as <2.5 g/day (<0.5 drink), 2.5–14.9 g/day (about 0.5–1 drink), 15–29.9 g/day (about 1–2.5 drinks), 30–60 g/day (about 2.5–5 drinks), and >60 g/day (≥5 drinks).

The outcome variables of interest were defined as the presence or absence of death from cardiovascular disease (that is, fatal cardiovascular or stroke events), incident coronary heart disease (fatal or non-fatal incident myocardial infarction, angina, ischaemic heart disease, or coronary revascularisation), death from coronary heart disease (fatal myocardial infarction or ischaemic heart disease), incident stroke (ischaemic or haemorrhagic events), or death from stroke. A secondary analysis was performed within these selected
Table 1 | Details of studies included in meta-analysis of association of alcohol consumption with selected cardiovascular disease outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Cohort designation</th>
<th>No of subjects</th>
<th>Country</th>
<th>Men (%)</th>
<th>Age range (years)</th>
<th>Study follow-up (years)</th>
<th>Outcomes measured</th>
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<tr>
<td>Albert et al 1999&lt;sup&gt;22&lt;/sup&gt;</td>
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<td>40–84</td>
<td>12</td>
<td>CHD mortality</td>
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<tr>
<td>Bazzano et al 2007&lt;sup&gt;23&lt;/sup&gt;</td>
<td>China National Hypertension Survey Epidemiology follow-up Study</td>
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<td>China</td>
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<td>240</td>
<td>8</td>
<td>Incident stroke and stroke mortality</td>
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<tr>
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<td>64 597</td>
<td>China</td>
<td>100</td>
<td>240</td>
<td>8</td>
<td>Incident CHD; CHD and CHD mortality</td>
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<tr>
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<td>Netherlands</td>
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<td>70</td>
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<td>40–84</td>
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<td>70–90</td>
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<td>CHD and CVD mortality</td>
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</table>
studies to determine the association between alcohol consumption and the risk of death from all causes.

Both reviewers independently extracted data from all studies fulfilling the inclusion criteria, and any disagreement was resolved by consensus. We extracted the data elements of cohort name, sample size, and population demographics (country, percentage male, mean age or age range). We also extracted information for key indicators of study quality in observational studies proposed by Egger et al.\(^{10}\) and Laupacis et al.\(^{12}\) for key indicators of study quality in observational studies.

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<table>
<thead>
<tr>
<th>Study</th>
<th>Cohort designation</th>
<th>No of subjects</th>
<th>Country</th>
<th>Men (%)</th>
<th>Age range (years)</th>
<th>Study follow-up (years)</th>
<th>Outcomes measured</th>
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<td>Lin et al 2005(^{72})</td>
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<td>100</td>
<td>40-55</td>
<td>5</td>
<td>Incident CHD</td>
</tr>
<tr>
<td>Marques-Vidal et al 2004(^{98})</td>
<td>PRIME Study—France</td>
<td>7352</td>
<td>France</td>
<td>100</td>
<td>50-59</td>
<td>5</td>
<td>Incident CHD</td>
</tr>
<tr>
<td>Murray et al 2002(^{90})</td>
<td>PRIME Study—Northern Ireland</td>
<td>2398</td>
<td>Ireland</td>
<td>100</td>
<td>50-59</td>
<td>5</td>
<td>Incident CHD</td>
</tr>
<tr>
<td>Mukamel et al 2003(^{105})</td>
<td>Multietnic cohort (Hawaii)</td>
<td>27 678</td>
<td>USA</td>
<td>50.1</td>
<td>&gt;30</td>
<td>NR</td>
<td>CHD and stroke mortality</td>
</tr>
<tr>
<td>Mukamel et al 2005(^{110})</td>
<td>Health Professionals Follow-up Study</td>
<td>38 077</td>
<td>USA</td>
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<td>40-75</td>
<td>12</td>
<td>Incident CHD and CVD mortality</td>
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<tr>
<td>Mukamel et al 2006(^{113})</td>
<td>Cardiovascular Health Study</td>
<td>4410</td>
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<td>Lung Health Study</td>
<td>3702</td>
<td>Canada</td>
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<td>Pedersen et al 2008(^{82})</td>
<td>Copenhagen City Heart Study</td>
<td>11 914</td>
<td>Denmark</td>
<td>44.3</td>
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<td>National Health and Nutrition Examination Study</td>
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<td>14.6</td>
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<tr>
<td>Renaud et al 1999(^{94})</td>
<td>Cohort from Centre de Medecine Preventive</td>
<td>36 250</td>
<td>France</td>
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<td>40-60</td>
<td>12-18</td>
<td>CHD and CVD mortality</td>
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<tr>
<td>Salonen et al 1983(^{105})</td>
<td>Two counties of eastern Finland</td>
<td>4063</td>
<td>Finland</td>
<td>100</td>
<td>30-59</td>
<td>7</td>
<td>Incident CHD</td>
</tr>
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<td>Sankai et al 2000(^{96})</td>
<td>Six Japanese communities</td>
<td>12 372</td>
<td>Japan</td>
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<td>40-69</td>
<td>9.4</td>
<td>Incident stroke</td>
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<td>Established populations for Epidemiologic Studies of the Elderly</td>
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<td>≥65</td>
<td>5</td>
<td>CVD mortality</td>
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<tr>
<td>Shaper et al 1987(^{98})</td>
<td>British Regional Heart Study</td>
<td>6103</td>
<td>UK</td>
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<td>Incident CHD</td>
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<tr>
<td>Simons et al 1996(^{79})</td>
<td>Dubbo Cohort of New South Wales</td>
<td>2805</td>
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<td>Nurses’ Health Study</td>
<td>121 700</td>
<td>USA</td>
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<td>30-55</td>
<td>NR</td>
<td>Incident CHD and CVD mortality</td>
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<tr>
<td>Suh et al 1992(^{31})</td>
<td>Multiple Risk Factor Intervention Trial</td>
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<td>CHD mortality</td>
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<tr>
<td>Suonen et al 1987(^{92})</td>
<td>Social Insurance Institution of Mobile Clinic Health Survey</td>
<td>4532</td>
<td>Finland</td>
<td>100</td>
<td>40-64</td>
<td>5</td>
<td>CHD mortality</td>
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<tr>
<td>Thun et al 1993(^{93})</td>
<td>Cancer Prevention Study II</td>
<td>489 626</td>
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<td>51.3</td>
<td>30-104</td>
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<td>CHD, CVD and stroke mortality</td>
</tr>
<tr>
<td>Tolstrup et al 2006(^{93})</td>
<td>Danish Cohort</td>
<td>53 500</td>
<td>Denmark</td>
<td>46.8</td>
<td>50-65</td>
<td>5.7</td>
<td>Incident CHD</td>
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<tr>
<td>Trevisan et al 2001(^{95})</td>
<td>Risk Factors and Life Expectancy Study</td>
<td>8647</td>
<td>Italy</td>
<td>100</td>
<td>30-59</td>
<td>7</td>
<td>CHD and CVD mortality</td>
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<tr>
<td>Trulsen et al 1998(^{106})</td>
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<td>13 329</td>
<td>Denmark</td>
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<td>45-84</td>
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<td>Valmadrid et al 1999(^{97})</td>
<td>Wisconsin Epidemiologic Study of Diabetic Retinopathy</td>
<td>983</td>
<td>USA</td>
<td>45.2</td>
<td>NR</td>
<td>12.3</td>
<td>CHD mortality</td>
</tr>
<tr>
<td>Waskiewicz et al 2004(^{78})</td>
<td>Pol-MONICA Programme</td>
<td>5452</td>
<td>Poland</td>
<td>49.3</td>
<td>35-64</td>
<td>NR</td>
<td>CVD mortality</td>
</tr>
<tr>
<td>Wellmann et al 2004(^{79})</td>
<td>MONICA Augsburg Cohort</td>
<td>2710</td>
<td>Germany</td>
<td>49.6</td>
<td>35-64</td>
<td>10</td>
<td>Incident CHD</td>
</tr>
<tr>
<td>Wilkins 2001(^{100})</td>
<td>National Population Health Survey</td>
<td>6014</td>
<td>Canada</td>
<td>43.8</td>
<td>≥40</td>
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<tr>
<td>Woo et al 1990(^{101})</td>
<td>Elderly Chinese Cohort</td>
<td>427</td>
<td>China</td>
<td>40</td>
<td>≥60</td>
<td>2.5</td>
<td>Incident stroke</td>
</tr>
<tr>
<td>Xu et al 2007(^{102})</td>
<td>Husbands from Shanghai Women’s Health Study</td>
<td>64 515</td>
<td>China</td>
<td>100</td>
<td>30-89</td>
<td>4.6</td>
<td>CHD and CVD mortality</td>
</tr>
<tr>
<td>Yang et al 1999(^{103})</td>
<td>South Bay Heart Watch Cohort</td>
<td>1196</td>
<td>USA</td>
<td>89</td>
<td>≥45</td>
<td>3.4</td>
<td>Incident CHD</td>
</tr>
<tr>
<td>Yuan et al 1997(^{104})</td>
<td>Four communities in Shanghai</td>
<td>18 244</td>
<td>China</td>
<td>100</td>
<td>45-64</td>
<td>6.7</td>
<td>CHD and stroke mortality</td>
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<tr>
<td>Zhang et al 2004(^{105})</td>
<td>Northern and southern Chinese populations</td>
<td>12 352</td>
<td>China</td>
<td>100</td>
<td>35-59</td>
<td>15.2</td>
<td>Incident stroke</td>
</tr>
</tbody>
</table>

CHD=coronary heart disease. CVD=cardiovascular disease.
Because these transformations can underestimate the variance of the relative risks derived from the odds ratios,⁴ ¹⁵ we performed a sensitivity analysis that excluded four studies for which this transformation had been applied. All analyses were performed with Stata 10.0 (StataCorp, College Station TX, USA). The Stata “metan” command was used to pool the ln(relative risks) across studies according to the DerSimonian and Laird random effects model.⁶⁶

In some studies, a single relative risk (or odds ratio) was not available for drinkers versus non-drinkers because the data were presented as only a dose-response (that is, several alcohol consumption levels relative to non-drinkers). In these cases, we first pooled across levels of intake within the study using a random effects model to derive a single relative risk for drinkers relative to non-drinkers. In these cases, we first pooled because the data were presented as only a dose-response (that is, several alcohol consumption levels relative to non-drinkers). In these cases, we first pooled across levels of intake within the study using a random effects model to derive a single relative risk for drinkers relative to non-drinkers. If the single relative risk was not available for drinkers versus non-drinkers because the data were presented as only a dose-response, we performed a sensitivity analysis excluding studies reporting only odds ratios. We conducted a cumulative meta-analysis of studies ordered chronologically to assess the sequential contributions of studies published over time.¹⁹ Finally, we assessed evidence of publication bias through visual inspection of funnel plots and Begg’s rank correlation test for asymmetry.²⁰ ²¹

**RESULTS**

**Identification of studies**

Our initial search yielded a total of 4235 unique citations (fig 1). After two rounds of reviews and searching citations of retained articles, we identified 131 studies as potentially relevant for analysis. For cardiovascular disease mortality and both end points, alcohol consumption was associated with lower risk, with relative risks of about 0.75 (table 2). In general, relative risks derived from the more highly adjusted and from the less adjusted analyses were similar. Figures 2–⁴ reveal little visual evidence of heterogeneity despite statistical evidence of heterogeneity (P<0.001, I²=72.2%), probably driven by the large number of participants (>100000) in studies included in the meta-analysis. Table 1 provides details of the included studies.²²–¹⁰⁵ Of these 84 studies, 34 (40%) reported on all-male cohorts, six (7%) reported on women only, and 44 (52%) included both men and women.

**Study quality**

We evaluated two primary features of study quality—the number of years that participants were followed and adjustment for confounding. Duration of follow-up for study end points ranged from 2.5 to 35 years, with a mean follow-up of 11 years (standard deviation 6 years) (table 1). Of the included studies, 13 (15%) had ≤5 years of follow-up. Similarly, studies varied in the degree of confounder adjustment, ranging from none to 18 variables, with a mean of six (SD 4). Most studies (68) presented adjusted estimates, but eight reported only unadjusted estimates and another eight adjusted only for basic demographic information. Methods of adjustment, effect measure, and confounding variables used in each study are presented in the appendix tables 1–5 on bmj.com for each of our primary outcomes.

**Primary analyses of cardiovascular disease mortality, coronary heart disease incidence and mortality, and stroke incidence and mortality**

For cardiovascular disease mortality and both end points for coronary heart disease, alcohol consumption was associated with lower risk, with relative risks of about 0.75 (table 2). In general, relative risks derived from the more highly adjusted and from the less adjusted results were similar. Figures 2–⁴ reveal little visual evidence of heterogeneity despite statistical evidence of heterogeneity (P<0.001, I²=72.2%), probably driven by the large number of participants (>100000) in studies included in the meta-analysis. Table 1 provides details of the included studies.²²–¹⁰⁵ Of these 84 studies, 34 (40%) reported on all-male cohorts, six (7%) reported on women only, and 44 (52%) included both men and women.

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Analyses of the dose of alcohol consumed showed that 2.5–14.9 g alcohol (about ≤1 drink) per day was protective for all five outcomes compared with no alcohol (table 2). For coronary heart disease outcomes, all levels of intake >2.5 g/day had similar degrees of risk reduction. For cardiovascular disease mortality as well as stroke incidence and mortality, the dose-response relations were less clear and more consistent with U or J shaped curves, suggesting an increased risk among drinkers of greater amounts of alcohol. Specifically, those who consumed >60 g/day were at a significantly increased risk of incident stroke compared with abstainers (relative risk 1.62 [1.32 to 1.98]).

Sensitivity analyses

In an analysis of differences in associations by sex, any amount of alcohol consumption relative to none was associated with greater reduction in cardiovascular disease mortality, stroke incidence, and stroke mortality for women than men. However, the association with stroke should be interpreted with caution, as the risk estimates for women are based on only three pooled studies. On the other hand, similar associations by sex were observed for coronary heart disease incidence and mortality (table 2).

Sensitivity analyses that were confined to only studies that controlled for the important confounders of smoking, age, and sex revealed generally similar results for all of the outcomes. Additional sensitivity analyses that account for the median number of confounding variables in the multivariable analyses of included studies revealed that those with fewer (less than the median) confounding variables generally reported slightly lower relative risk estimates. However, this pattern was inconsistent across the outcomes. Specifically, an increased risk of stroke mortality was observed for studies with limited adjustment for confounding. A similar trend was observed when considering the duration of follow-up. Using the pooled median number of years as the cut point, we found that studies with shorter follow-up reported a greater risk reduction for all outcomes except cardiovascular disease and coronary heart disease mortality (table 2).

Among those studies that used long term abstainers as the referent category, excluding former drinkers or evaluating them separately, the estimated association between drinking and both incidence and mortality estimates did not change substantively (table 2). Among studies that evaluated former drinkers separately, the risk of death (from cardiovascular disease and coronary heart disease) was significantly higher in former drinkers than in drinkers. However, former drinkers did not have an increased risk of incident cardiovascular events (coronary heart disease or stroke).

All the point estimates were <1.0 in studies, except for one study for cardiovascular disease mortality and two studies for coronary heart disease incidence and mortality.

In contrast, the overall associations of alcohol intake with stroke incidence and mortality were close to null, both in minimally adjusted and more highly adjusted models (table 2, figs 5 and 6). However, this null association seemed to obscure nearly significant but opposite associations with subtypes of incident stroke. Among the 12 studies on incident haemorrhagic stroke, the pooled relative risk for current alcohol drinkers compared with non-drinkers was 1.14 (95% confidence interval 0.97 to 1.34), whereas the eight studies on ischaemic stroke showed a moderate reduction in the pooled relative risk of 0.92 (0.85 to 1.00). Alcohol use was not associated with stroke mortality, but few studies assessed the risk of mortality from haemorrhagic or ischaemic stroke separately. Furthermore, only two studies reported relative risks on stroke end points for former drinkers compared with non-drinkers.
Finally, a sensitivity analysis that excluded the few studies where only odds ratios instead of relative risks were presented had little effect on the results. In cumulative meta-analyses of cardiovascular disease and coronary heart disease outcomes (appendix figs 1–3 on bmj.com), there was little variation in the relative risk associated with alcohol consumption on cardiovascular disease mortality or incident coronary heart disease with addition of new studies after 1999; for coronary heart disease mortality, this plateau in incremental change from new studies occurred as early as 1992–3.

Mortality from all causes

Of the 84 studies addressing alcohol and cardiovascular disease events, 31 also examined the association of alcohol consumption with all cause mortality. The pooled estimates from these studies showed a lower risk of all cause mortality for drinkers compared with non-drinkers (relative risk 0.87 (0.83 to 0.92)) (fig 7). However, the association was J shaped, with the lowest risk for those consuming 2.5–14.9 g/day (relative risk 0.83 (0.80 to 0.86), 16 studies) and an elevated risk in those consuming >60 g/day (relative risk 1.30 (1.22 to 1.38), 8 studies).

Publication bias

Visual inspection of the funnel plot for each outcome did not show asymmetry, an indication that significant publication bias was not likely. This was further confirmed by a non-significant Begg’s test for each outcome (for cardiovascular disease mortality, P=0.40; incident coronary heart disease, P=0.75; coronary heart disease mortality, P=0.089; incident stroke, P=0.33; stroke mortality, P=0.59; all cause mortality, P=0.26).

DISCUSSION

In this review of 84 studies of alcohol consumption and cardiovascular disease, alcohol consumption at 2.5–14.9 g/day (about ≤1 drink a day) was consistently associated with a 14–25% reduction in the risk of all outcomes assessed compared with abstaining from alcohol. Such a reduction in risk is potentially of clinical importance, but consumption of larger amounts of alcohol was associated with higher risks for stroke incidence and mortality.

To our knowledge, this systematic review and meta-analysis is the most comprehensive to date. Although roughly similar estimates of lower risk were observed in previous meta-analyses of both coronary heart disease and stroke,1,2 our review extends the findings by assessing a broader array of relevant cardiovascular outcomes and adding several new important studies. Our review clarifies several discrepancies among prior reports. Corrao et al reported a J shaped relation between alcohol intake and coronary heart disease,2 whereas the review by Maclure described this relation as L shaped because he did not observe an increase in coronary heart disease risk associated with higher alcohol consumption.6 Our updated meta-analysis supports the latter association for coronary heart disease, with a 25–35% risk reduction for light to moderate drinking106 that also is present with heavier drinking.

Our analysis of multiple cardiovascular outcomes also shows the complexities inherent in the study of alcohol consumption. Modest alcohol intake was associated with lower stroke incidence and mortality, but the risk increased substantially with heavier drinking (that is, a J shaped relation). Furthermore, the association of alcohol consumption is complex and differs by stroke subtype, with a slightly lower risk of ischaemic stroke but higher risk of haemorrhagic stroke. These differential associations probably reflect the known antithrombotic effects of alcohol.107 Alcohol consumption, particularly at high doses, also seems to have an adverse association with blood pressure that may account, in part, for the higher risk of haemorrhagic stroke associated with heavier drinking.108 Additionally, our analysis does not consider other known detrimental effects of high alcohol consumption.4 Therefore, our findings lend further support for limits on alcohol consumption.106 109

Table 2

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative risk (95% CI)</th>
<th>Weight (%)</th>
<th>Relative risk (95% CI)</th>
</tr>
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<tr>
<td>Blackwelder et al 1980</td>
<td>2.63 (0.54 to 0.79)</td>
<td>1.94</td>
<td>0.72 (0.44 to 1.19)</td>
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<td>Colditz et al 1985</td>
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<td>0.70 (0.40 to 1.00)</td>
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<td>Friedman et al 1986</td>
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<tr>
<td>Kono et al 1986</td>
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<td>5.12</td>
<td>0.82 (0.79 to 0.86)</td>
</tr>
<tr>
<td>Suheren et al 1987</td>
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<td>0.72 (0.52 to 0.98)</td>
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<td>5.00</td>
<td>0.82 (0.76 to 0.88)</td>
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<td>0.86 (0.69 to 1.09)</td>
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<td>Cullen et al 1993</td>
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<td>2.49</td>
<td>0.59 (0.40 to 0.89)</td>
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<tr>
<td>Rehm et al 1999</td>
<td>3.08 (0.61 to 0.83)</td>
<td>5.97</td>
<td>0.77 (0.26 to 2.22)</td>
</tr>
<tr>
<td>Thun et al 1999</td>
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<td>2.53</td>
<td>0.60 (0.40 to 0.88)</td>
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<tr>
<td>Yuan et al 1997</td>
<td>4.68 (0.71 to 0.81)</td>
<td>3.28</td>
<td>0.86 (0.64 to 1.15)</td>
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<tr>
<td>Maskarinec et al 1998</td>
<td>2.49 (0.66 to 0.76)</td>
<td>4.29</td>
<td>1.02 (0.64 to 1.63)</td>
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<td>Albert et al 1995</td>
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<td>2.09</td>
<td>0.70 (0.40 to 1.00)</td>
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<td>Renaud et al 1995</td>
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<td>0.95 (0.86 to 1.06)</td>
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<td>Valmadrid et al 1997</td>
<td>4.82 (0.81 to 0.72)</td>
<td>4.70</td>
<td>0.81 (0.72 to 0.92)</td>
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<tr>
<td>Solomon et al 2000</td>
<td>1.94 (0.72 to 0.44)</td>
<td>1.00</td>
<td>0.75 (0.68 to 0.81)</td>
</tr>
<tr>
<td>Trevisan et al 2001</td>
<td>100.00 (0.001, 1.00)</td>
<td>0.75 (0.68 to 0.81)</td>
<td></td>
</tr>
</tbody>
</table>

*Weight from random effects analysis

Fig 4 | Forest plot of mortality from coronary heart disease associated with alcohol consumption
Table 2 | Stratified analyses of pooled relative risks (95% CI) for cardiovascular and stroke outcomes (number of pooled studies in parentheses after each effect estimate)

<table>
<thead>
<tr>
<th>Active drinkers v non-drinkers:</th>
<th>Coronary heart disease</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Least adjusted models</td>
<td>0.84 (0.75 to 0.95) (11)</td>
<td>0.80 (0.70 to 0.91) (10)</td>
</tr>
<tr>
<td>Most adjusted models</td>
<td>0.75 (0.70 to 0.80) (21)</td>
<td>0.71 (0.66 to 0.77) (29)</td>
</tr>
<tr>
<td>Active drinkers v lifetime abstainers</td>
<td>0.82 (0.78 to 0.86) (9)</td>
<td>0.73 (0.61 to 0.88) (9)</td>
</tr>
<tr>
<td>Former drinkers v non-drinkers</td>
<td>1.48 (1.23 to 1.79) (6)</td>
<td>1.10 (0.91 to 1.33) (8)</td>
</tr>
</tbody>
</table>

Adjustment for confounding factors:
- Sex:
- Median follow-up time: Short
- Median follow-up time: Long

Our review also highlights other important aspects of the relation between alcohol consumption and cardiovascular disease. Firstly, the lower risk of coronary heart disease associated with alcohol consumption was at least as strong for women as for men. Limited evidence suggests that the risk of stroke related to alcohol is lower for women than men, but this may only reflect lower alcohol intake among women. Secondly, inclusion of former drinkers did not seem to bias the association of alcohol consumption with cardiovascular disease. Thirdly, when studies were summarised chronologically, we found that the overall association between drinking and cardiovascular disease and coronary heart disease became apparent at least a decade ago, and ongoing studies have done little to revise the estimated associations.

An argument for causation
From the extensive body of literature summarised here, the association between alcohol consumption and decreased cardiovascular risk is not in question, as additional research has not changed this conclusion. Rather, the lingering question is whether this association is causal. Clearly, observational studies cannot establish causation. However, when the present results are coupled with those from our companion review paper summarising interventional mechanistic studies.
Study Relative risk

- Blackwelder et al 1980
- Kono et al 1986
- Hansagl et al 1995
- Thun et al 1997
- Yuan et al 1997
- Maskarinec et al 1998
- Gaziano et al 2000
- Jakovicic et al 2004
- Bazzano et al 2007
- Hart et al 2008
- Deev et al 1998
- Maskarinec et al 1998
- Simons et al 1996
- Fuchs et al 1995
- Berberian et al 1994
- Cullen et al 1993
- Berbarian et al 1994
- Gronbaek et al 1995
- Fuchs et al 1994
- Simons et al 1996
- Maskarinec et al 1998
- Deev et al 1998
- Deev et al 1998
- Renaud et al 1999
- Jamrozik et al 2000
- Gaziano et al 2000
- Trevisan et al 2001
- Diem et al 2003
- Wellmann et al 2004
- Jakovicic et al 2004
- Knoops et al 2004
- Waskiewicz et al 2004
- Lin et al 2005
- Doll et al 2005
- Gun et al 2006
- Xu et al 2007
- Pedersen et al 2008
- Hart et al 2008
- Djoussé et al 2009

Overall: P=0.001, I²=68.0%

Fig 6 | Forest plot of mortality from stroke associated with alcohol consumption

Study Relative risk

- Blackwelder et al 1980
- Colditz et al 1985
- Kono et al 1986
- Friedman et al 1986
- Suhonen et al 1987
- Kivela et al 1989
- Boffetta et al 1990
- Scher et al 1992
- Cullen et al 1993
- Berberian et al 1994
- Gronbaek et al 1995
- Fuchs et al 1994
- Simons et al 1996
- Maskarinec et al 1998
- Deev et al 1998
- Deev et al 1998
- Renaud et al 1999
- Jamrozik et al 2000
- Gaziano et al 2000
- Trevisan et al 2001
- Diem et al 2003
- Wellmann et al 2004
- Jakovicic et al 2004
- Knoops et al 2004
- Waskiewicz et al 2004
- Lin et al 2005
- Doll et al 2005
- Gun et al 2006
- Xu et al 2007
- Pedersen et al 2008
- Hart et al 2008
- Djoussé et al 2009

Overall: P=0.001, I²=73.1%

Fig 7 | Forest plot of mortality from all causes associated with alcohol consumption

Highlighting on biomarkers associated with cardiovascular disease, the argument for causation becomes more compelling. Indeed, the mechanistic biomarker review shows biological plausibility for a causal association by showing favourable changes in pathophysiologically relevant molecules.

Therefore, we can now examine the argument for causation based on Hill’s criteria. Beyond the biological plausibility argument discussed above, there is an appropriate temporal relation with alcohol use preventing cardiovascular disease. Secondly, we have observed a greater protective association with increasing dose, except that it seems to be offset somewhat by negative associations with the risk of haemorrhagic stroke. Thirdly, the protective association of alcohol has been consistently observed in diverse patient populations and in both women and men. Fourthly, the association is specific: moderate drinking (up to 1 drink or 12.5 g alcohol per day for women and 2 drinks or 25 g alcohol per day for men) is associated with lower rates of cardiovascular disease but is not uniformly protective for other conditions, such as cancer. Lastly, the reduction in risk is notable even when controlling for known confounders (such as smoking, diet, and exercise). Any potential unmeasured confounder would need to be very strong to explain away the apparently protective association.

Limitations of study

The results of our meta-analysis should be interpreted in context of the limitations of available data. Firstly, the quality of individual studies varied, with some studies having limited follow-up and limited adjustment for potential confounding. With respect to study follow-up, it is possible that misclassification of alcohol consumption may increase with study length because of changes in drinking habits over time. It is also possible that potential biological effects of alcohol vary with time of exposure. However, arguing against both these possibilities, the analysis stratified by length of follow-up did not show different associations between alcohol intake and outcome for shorter follow-up times versus longer times.

Secondly, only a limited subset of studies provided specific risk estimates for different beverages. Although there is great interest in differences between wine, beer, and spirits, alcoholic drinks generally have similar effects on high density lipoprotein cholesterol, and it is likely that any particular benefit is seen in context of the limitations of available data. Firstly, the quality of individual studies varied, with some studies having limited follow-up and limited adjustment for potential confounding. With respect to study follow-up, it is possible that misclassification of alcohol consumption may increase with study length because of changes in drinking habits over time. It is also possible that potential biological effects of alcohol vary with time of exposure. However, arguing against both these possibilities, the analysis stratified by length of follow-up did not show different associations between alcohol intake and outcome for shorter follow-up times versus longer times.

Thirdly, we found only limited information on the relationship between alcohol intake and mortality from subtypes of stroke, so this topic continues to be important for large observational cohort studies. Finally, we observed significant heterogeneity across studies for several of our pooled analyses. This may be due in great part to large study sample sizes, which can confound greater statistical power to heterogeneity tests, whereas the clinical relevance of this heterogeneity may be...
WHAT IS ALREADY KNOWN ON THIS TOPIC:
Systematic reviews have addressed the association of alcohol consumption with various cardiovascular outcomes. However, these reviews are somewhat out of date, and none has comprehensively studied a broad spectrum of relevant cardiovascular end points.

WHAT THIS STUDY ADDS:
This meta-analysis provides a summary of current knowledge regarding alcohol associations with six meaningful clinical end points—cardiovascular disease mortality, coronary heart disease incidence and mortality, stroke incidence and mortality, and all-cause mortality. The results confirm the beneficial effects of moderate alcohol consumption and the need to elucidate the underlying pathophysiological mechanisms.

The debate on how to integrate this evidence into clinical practice and public health messages will require integration of all possible effects of alcohol—from injury and violence to glucose metabolism and inflammation—and recognition that these effects may be distributed unequally across the population. For example, injury risk probably disproportionately affects younger individuals, whereas cardiovascular disease mainly affects older adults. Robust studies that examine multiple outcomes simultaneously are needed to identify those subsets of the population in which reduced cardiovascular risk might dominate against those for whom the risks of social and medical problems (including several cancers and injury) are too great. Despite the latter concerns, results of our secondary analysis of overall mortality (fig 5) support the notion that moderate alcohol consumption is associated with net benefit, at least in populations similar to those studied in the extant literature.

Our two systematic review papers summarise a surprisingly extensive body of literature on the relation between alcohol and cardiovascular disease. Our findings point to the need to define implications for clinical and public health practice. These reviews and the perspectives above provide a foundation for that dialogue.

Preliminary results from this manuscript were presented at the 32nd annual meeting of the Society of General Internal Medicine, Miami, Florida, 14 May 2009.

Contributors: All authors conceived the study and developed the protocol. PER and SEB conducted the search, abstracted the data for the analysis, and performed the statistical analysis. PER, SEB, and WAG wrote the first draft of the manuscript. All authors had access to the data, critically reviewed the manuscript for important intellectual content, and approved the final version of the manuscript. WAG will act as guarantor for the paper.

Funding: This work was supported by a contracted operating grant from Program of Research Integrating Substance Use Information into Mainstream Healthcare (PRISU) funded by the Robert Wood Johnson Foundation, project No 58529; with cofunding by the Substance Abuse and Mental Health Services and the Administration Center for Substance Abuse Treatment. PER is supported by a Frederick Banting and Charles Best Canada Graduate Scholarship from the Canadian Institutes of Health Research. SEB is supported by a Postdoctoral Fellowship Award from the Alberta Heritage Foundation for Medical Research. WAG is supported by a Canada Research Chair in Health Services Research and by a Senior Health Scholar Award from the Alberta Heritage Foundation for Medical Research. The study was conducted independently of funding agencies. None of the funding agencies played an active role in the preparation, review, or editing of this manuscript.

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: support from the Robert Wood Johnson Foundation, the Substance Abuse and Mental Health Services and the Administration Center for Substance Abuse Treatment; PER is supported by a Frederick Banting and Charles Best Canada Graduate Scholarship from the Canadian Institutes of Health Research; SEB is supported by a Postdoctoral Fellowship Award from the Alberta Heritage Foundation for Medical Research; WAG is supported by a Canada Research Chair in Health Services Research and by a Senior Health Scholar Award from the Alberta Heritage Foundation for Medical Research. The study was conducted independently of funding agencies. None of the funding agencies played an active role in the preparation, review, or editing of this manuscript.

Ethical approval: Not required.

Data sharing: Statistical code and datasets available from the corresponding author at wghai@ucalgary.ca


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Accepted: 12 December 2010